IV. REMARKS

Claim Status

Claims 2-4, 6, 9-35 are pending. Claims 13 and 35 have been cancelled. Claims 2, 25 have been amended. Clai. 36 and 37 are new.

Specification

The disclosure is objected to because of the following informalities: The specification on page 3 states that a healthy person (normal blood) has about 5% of total circulating fibrinogen of the Fib420 variety. On page 4, it is stated that in blood of healthy persons, about 70% is in the HMW form (340kDa), 26% in LMW form (305kDa), and 4% in LMW' form (270kDa). This adds up to 100%, but the statements are contradictory because 5% should be in Fib420 form, but this 5% is not accounted for in the total fibrinogen content of blood of a normal person. Appropriate clarification is required.

Applicants appreciate the examiner's highlighting this anomaly in the specification. The Examiner is right, in healthy persons normally only traces of Fib420 fibrinogen occur, although in some special cases a few % of Fib420 may occur. The text on page 3, line 20 should have stated more correctly - and has now been amended to state - that in normal persons only traces of Fib420 are present and only in exceptional cases Fib420 levels as high as 5% have been found.

Claim Rejections - 35 USC § 112, first paragraph, enablement

Claims 2-4, 6, 9, 11-13, 25-35 stand rejected under 35

U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for modifying the properties of a fibrin matrix, does not reasonably provide enablement for an *in vivo* method, specifically claimed in claims 11-13, 35.

As noted by the examiner, the application states, "To date the enzyme which converts HMW to LMW and LMW' has not been identified" (page 4). This is a statement with regard to the state of the art at the time of invention. If the enzyme which converts one form of fibrinogen to another is not even known, the examiner states that it follows that how to vary the activity of an unknown enzyme *in vivo* in order to modify *the* concentration of circulating variants of fibrinogen is also unknown.

Therefore, the examiner concludes that manipulation of the forms of fibrinogen *in vivo is* not enabled since neither the specification nor the prior art provides enablement for the claimed *in vivo* method.

Applicants respectfully suggest that this rejection may be based on a misunderstanding of the claimed in vivo method. Even though, in the in vivo method, the formation of the fibrin matrix occurs in vivo, this is preceded by an in vitro modification of the fibrinogen after which the in vitro modified fibrinogen is applied at a place in the body where the formation of a fibrin matrix is desired.

The local fibrin matrix formation may occur automatically or be promoted by simultaneous application of enzyme (thrombin) and/or other factors promoting conversion of fibrinogen into

fibrin (factor X1lIa, CaCl2). Thus, the modification of the fibrin matrix is a result of a modification of the composition of the fibrinogen from which the fibrin matrix is formed. In the present invention, the step of modifying the composition of the fibrinogen is always an in vitro stop.

To clarify the same, applicant has modified claim 25 to clarify that modifying the fibrinogen content in step (b) is performed in vitro.

Claim 11 has been amended in like manner adding the phrase "obtained after the in vitro modification step (b)".

Claim Rejections - 35 USC 112, 2nd paragraph, indefinite

Claims 2-4, 6, 9, 11-13, 25-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because they depend on a varying composition of fibrinogen variants as the starting material.

The examiner bases this rejection on the principle that a claim may be rendered indefinite by reference to an object that is variable. For example, the Board has held that a limitation in a claim to a bicycle that recited "said from and rear wheels so spaced as to give a wheelbase that is between 58 and 75 percent of the height of the rider that the bicycle was designed for" was indefinite because the relationship of parts was not based on any known standard for sizing a bicycle to a rider, but on a rider of unspecified build. *Ex parte Brummer,* 12 USPQ2d 1654 (Bd. Pat. App. & Inter. 1989).

The second ground of rejection (page 4 in the middle) is that

the pending claims are indefinite (unclear) because they refer to a step of modifying the composition of a fibrinogen mixture where the starting composition is variable.

Applicant traverses this ground for rejection.

The decision of the Board in *Ex parte Brummer*, cited by the examiner, is pertinent as it is founded on the incontrovertible principle of law that "The purpose of 35 USC 112 is to allow the public to know exactly what the patent covers, …". [12 USPQ2d 1654], 1655 Based on this principle the court concludes "In the case before us here, it is our opinion that one would be at a loss to determine whether a particular bicycle is covered …" [12 USPQ2d 1654, 1655].

In other words because a determination of whether a bicycle [a product] infringed the claims required reference to an extrinsic fact [the height of the cyclist] the claim was indefinite.

The present claims are method claims. No reference to intrinsic evidence is required to determine if the claim is infringed – either one practiced the modification step of one did not. The constituents of the material on which the action is being taken [% of each component] do not enter into the infringement analysis and unlike Brummer one would not "would be at a loss to determine whether a particular" process is covered.

Claim Rejections – 35 USC § 102(b)

Claims 2-4, 6, 9, 25-34 stand rejected under 35 USC 102(b) as being clearly anticipated by WO 00/62833 [N] or US 6,946,140 or Holm et al. or Hasegawa et al., Smith et al. or Falls et al.

The claims are directed to a method comprising:

a) selecting a composition consisting of multiple variants of fibrinogen (of which one is HMW fibrinogen),

b) modifying the fibrinogen to change the relative concentration of at least one variant, and

c) forming a fibrin matrix from the composition of step b).

The examiner comments in the office action that since applicant states the response to the restriction requirement that there is HMW in some amount in all the elected claim methods, a change in any concentration of any variant will necessarily cause a change in the relative concentration of the HMW variant.

This conclusion does not logically follow. It is true that in a 2 component system a rise in the level of one component would necessarily result in a decrease in the other, but since this is a more than 2 component system, a change in the level of one component may not necessarily cause any change in one of the other components.

As stated by the examiner, Clark et al., WO 00/62833, discloses in Example 1, page 29, normal plasma which contains a mixture of fibrinogen types, precipitation by glycine, precipitation by ammonium sulfate 25% saturation which produces a purified fibrinogen with a mixture of types as evidence by fibrinogen bands I and II.

Although Clark et al. does discloses the presence of various fibrinogen forms in plasma and ways to isolate various forme

and studies clottability, Clark never shows or mentions any effect of the fibrinogen composition in relation to angiogenesis.

Clark et al., US 6,946,140, also fractionates fibrinogen ppt. from normal plasma and produces fibrin gels from the various fractions and tests the gels for fibroblast migration activity. See Examples 1 and 2.

The ‘140 patent discloses methods for enhancing fibroblast migration in wounds by a fibrinogen preparation including a lipid rich component but does not reveal or even hints to effects of the fibrinogen composition (HMW/LMW ratio) on this effect.

Furthermore no disclosure pointing to an effect on angiogenesis is made.

Holm et al. fractionates plasma fibrinogen in HMW, LMW and LMW’ fractions and study effects on clot formation but no effects on angiogenesis are shown or suggested.

Hasegawa et al. also fractionate fibrinogen in the various forms and perform a detailed clotting study, again without even hinting to angiogenesis.

Smith et al. use fibrinogen fractions to study dot retraction and do not reveal or hint to effects on angiogenesis.

Falls at al. make fibrin clots of various fibrinogen fractions and study the dissolution of these clots by t-PA relating this to clot composition. No effects on angiogenesis are shown or mentioned.

In conclusion the referred prior art describes the existence *of*

various fibrinogen forms, ways to isolate and partially purify *the* various forms and shows some differences *of* the various forms in a number of processes. Nowhere in this prior art effects an angiogenesis are studied or even mentioned.

Claim Rejections – 35 USC § 103(a)

Claims 2-4, 6, 9, 11-13, 25-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/62833 or US 6,946,140 or Holm et al. or Hasegawa et al., Smith et al. or Falls et al.

None of these references disclose or suggest the angiogenesis effect of modifying fibrinogen content. Claims 2 and 6 stand rejected as merely reciting desired results and as such are also rejected over the references of record. Claim 25 has been amended to recite more than an intended result and thus the dependent claims no longer refer only to an intended result but rather a process.

One of ordinary skill in the art would not have recognized the angiogenesis effect of modifying the fibrinogen level and thus would not have been motivated at the time of invention to produce this composition in order to obtain the results.

Conclusion

Favorable reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge payment for any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

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